Higher serum magnesium levels associated with the use of sodium–glucose cotransporter 2 (SGLT2) inhibitors among type 2 diabetes patients: a meta-analysis of randomized controlled trials

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Abbreviations

CENTRAL	Cochrane Central Register of Controlled Trials
CI	Confidence interval
CKD	Chronic kidney disease
SD	Standard deviation
SGLT2	Sodium glucose cotransporter 2
RCTs	Randomized controlled trials
UGE	Urinary glucose excretion
WMD	Weighted mean difference

Abstract

Aim/hypothesis To examine whether and to what extent sodium glucose cotransporter 2 (SGLT2) inhibitors affect serum electrolyte levels in type 2 diabetes patients by synthesizing available evidence from randomized controlled trials (RCTs).

Methods We searched PubMed, Embase, CENTRAL, and ClinicalTrials.gov up to May 24, 2016 for published RCTs of SGLT2 inhibitors that reported changes in serum electrolyte levels. Weighted mean difference (WMD) between each SGLT2 inhibitor and placebo was calculated using random-effects model. Dose-dependent relationships in each SGLT2 inhibitor were evaluated using meta-regression analysis.

Results Eighteen eligible RCTs, including 15,309 patients and four SGLT2 inhibitors (canagliflozin, dapagliflozin, empagliflozin, and ipragliflozin) were evaluated. In patients without chronic kidney disease, each SGLT2 inhibitor significantly increased serum magnesium levels as compared with placebo (canagliflozin: WMD 0.06 mmol/l for 100 mg and 0.09 mmol/l for 300mg; dapagliflozin: WMD 0.1 mmol/l for 10 mg; empagliflozin: WMD 0.04 mmol/l for 10 mg and 0.07 mmol/l for 25 mg; and ipragliflozin: WMD 0.05 mmol/l for 50 mg). Canagliflozin seemed to increase serum magnesium in a linear dose-dependent manner (p=0.10). Serum phosphate was significantly increased by dapagliflozin, but serum sodium appeared to significantly differ by SGLT2 inhibitor type. No significant changes in serum calcium and potassium were observed. Findings were robust after including trials involving patients with chronic kidney disease.

Conclusions/interpretation SGLT2 inhibitors marginally increased serum magnesium levels among type 2 diabetes patients, indicating a drug class effect. Further

investigation is required to examine the clinical significance of elevating magnesium levels among type 2 diabetes patients.

Introduction

Electrolyte abnormalities, usually caused by renal impairment, can lead to serious complications and even death. Sodium glucose cotransporter 2 (SGLT2) inhibitors are a novel class of glucose-lowering agents for treating type 2 diabetes by selectively inhibiting renal glucose reabsorption and increasing urinary glucose excretion (UGE) [1]. Because of increased UGE, SGLT2 inhibitor treatment may result in osmotic diuresis, which may trigger volume depletion and dehydration [2]. However, little is known about whether such hemodynamic changes caused by SGLT2 inhibitors influence renal electrolyte handling in patients with type 2 diabetes. We conducted a meta-analysis to synthesize available evidence from randomized controlled trials (RCTs) to examine whether and to what extent SGLT2 inhibitors affect serum electrolyte levels in patients with type 2 diabetes.

Methods

Search strategy and selection of articles We searched PubMed, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), and ClinicalTrials.gov up to May 24, 2016 to identify eligible RCTs by using relevant search terms without restriction of language and year of publication (see ESM Table 1 for a complete list of search terms). We included parallel RCTs of at least 24 weeks' duration that compared SGLT2 inhibitors to placebo in adult patients with type 2 diabetes and reported mean (percent) changes from baseline of electrolyte levels in each group or other data to calculate these variances. Our primary outcomes were serum magnesium and secondary outcomes included serum sodium, phosphate, potassium, and calcium.

Data extraction and quality assessment We collected the following information from

each eligible RCT: first author (publication year), study characteristics (country of origin, design, and funding), patients' characteristics (inclusion criteria, background treatments, mean age, pre-existing CKD disease, race, baseline glycated haemoglobin (HbA_{1c}), mean estimated glomerular filtration rate, and body mean index), interventions (type and dose of SGLT2 inhibitor), and the mean values (electrolyte level), variance measure, and the number of participants in the treatment and control arms for all reported periods. Mean (standard deviation) changes from baseline (mmol/l) for each SGLT2 inhibitor were extracted except canagliflozin, of which data were presented as mean (standard deviation) percent change from baseline (%) in the original article. The Cochrane risk of bias tool was used to assess the quality of RCTs based on 5 domains: random sequence generation (selection bias), allocation concealment (selection bias), blinding (performance bias and detection bias), incomplete outcome data (attrition bias), and selective reporting (reporting bias). Two reviewers (HT and XZ) independently extracted the data and assessed the quality of each RCT. Any disagreements were resolved by consensus or referral to a third reviewer (YS).

Statistical analysis Weighted mean differences (WMD) of serum electrolyte levels between each SGLT2 inhibitor and placebo with 95% confidence interval (CI) were calculated, using random effects meta-analysis models, evaluating each SGLT2 inhibitor separately, and by dose. Heterogeneity was quantified using the I^2 statistic, with I^2 of 25, 50, and 75 indicating low, medium, and high heterogeneity, respectively. A meta-regression analysis was employed to investigate any possible dose-dependent relationships between doses of each SGLT2 inhibitor and changes in serum electrolyte

levels [3]. The main meta-analysis was performed in patients without CKD. A sensitivity analysis additionally including the trials involving patients with CKD was performed. Publication bias was assessed using Begg's test. All statistical analyses were performed with STATA (Version 14; Stata Corp., College Station, TX).

Results

Of 1,874 articles screened, 18 trials met eligibility criteria (ESM Fig 1), totaling 15,309 unique participants [4-21]. Four SGLT2 inhibitors (canagliflozin, dapagliflozin, empagliflozin, and ipragliflozin) were evaluated. The duration of interventions ranged from 24 to 160 weeks (mean weeks: 67). Participants were generally middle-aged (mean age: 58), whites (14/18 studies), without CKD (16/18 studies) (ESM Table 2). Electrolyte concentrations at baseline fell within normal reference ranges in all studies (ESM Table 3). Most included trials were judged as having a low risk of bias, except for one trial with high risk of bias for lacked blinding [10] (ESM Fig. 2).

Serum magnesium levels significantly increased among canagliflozin users than among those receiving placebo (100 mg: WMD 8.03%, 95% CI: 6.89 to 9.16; 300 mg: WMD 11.06%, 95%CI: 9.92 to12.19) (Fig 1). Canagliflozin seemed to increase serum magnesium in a dose- dependent manner (P for linear trend=0.10). Compared with placebo, only dapagliflozin 10 mg significantly increased serum magnesium (WMD 0.10 mmol/l, 95%CI: 0.01 to 0.19). Empagliflozin significantly raised serum magnesium (10 mg: WMD: 0.04 mmol/l, 95% CI: 0.02 to 0.07; 300 mg: WMD: 0.07 mmol/l, 95%CI: 0.04 to 0.09), as did ipragliflozin 50 mg (WMD 0.05 mmol/l, 95%CI: 0.03 to 0.08). A sensitivity analysis additionally including 2 trials involving CKD patients showed that the results were robust. Statistically significant between-study heterogeneity was evident for

dapagliflozin and empagliflozin (I^2 >75%) but not for canaglifozin (I^2=0%). There was no evidence of publication bias in this meta-analysis for serum magnesium (p>0.05).

Compared with placebo, dapagliflozin 5 mg (WMD 0.04 mmol/l, 95%CI: 0.01 to 0.06) and dapagliflozin 10 mg (WMD 0.05 mmol/l, 95%CI: 0.02 to 0.09) significantly increased serum phosphate (Table 1 and ESM Fig. 3). Serum sodium levels were significantly higher among empagliflozin 25 mg users than among those receiving placebo (WMD 0.31 mmol/l, 95%CI: 0.04 to 0.58). However, canagliflozin 300 mg seemed to decrease serum sodium levels (WMD -0.36 mmol/l, 95%CI: -0.68 to -0.05) (Table 1 and ESM Fig. 4). No significant changes in serum calcium levels and potassium levels were observed among the patients using SLGT2 inhibitors (Table 1, ESM Fig. 5, and ESM Fig.6). A dose dependence relationship between doses of each SGLT2 inhibitors and these electrolytes levels was not observed. When additionally including the trials involving CKD patients, results were similar, except the comparison between empagliflozin 10 mg and placebo on change of serum sodium levels was significant (WMD 0.26 mmol/l, 95%CI: 0.03 to 0.49). Heterogeneity was variable across SGLT2 type, doses, and electrolyte levels (Table 1).

Discussion

Our meta-analysis of 18 RCTs involving 15,309 patients provides the first robust evidence that SGLT2 inhibitors significantly increase serum magnesium levels among patients with type 2 diabetes; on average, serum magnesium levels were raised by 0.06 mmol/l for canagliflozin 100 mg and 0.09 mmol/l for canagliflozin 300 mg, 0.1 mmol/l for dapagliflozin 10 mg, 0.04 mmol/l for empagliflozin 10 mg and 0.07 mmol/l for

empagliflozin 25 mg, and 0.05 mmol/l for ipragliflozin 50 mg. Taken together, the evidence indicates a drug class effect on serum magnesium levels. Effects on serum phosphate levels and serum sodium levels appear to differ by SGLT2 inhibitor type and dose. No significant effects on serum calcium levels and serum potassium levels were observed.

Given that SGLT2 inhibitors induce glucosuria and osmotic diuresis, which may trigger volume depletion and dehydration, we hypothesized that changes in circulating electrolyte levels might occur with the use of such a new class of drugs. The significant elevation in serum magnesium levels, and the possibly increased phosphate levels, might be the result of osmotic diuresis caused by SGLT2 inhibitors, but the precise mechanisms are unknown. Abnormally high magnesium levels are predictive of total mortality in patients with heart failure [22], critically ill patients [23], and in those receiving haemodialysis [24]. Therefore, caution must to be exercised in those patients with disturbed renal function, such as severe CKD. On the other hand, in the general population and in those with type 2 diabetes, a gradient of risk for cardiovascular disease has been observed across the normal serum magnesium concentration range [25], with high-normal concentrations of serum magnesium associated with a lower risk of events [25]. Our meta-analysis found that a mean increase of 0.05 mmol/l in serum magnesium was significantly associated with a reduction in systolic blood pressure by 2.00 mm Hg and diastolic blood pressure by 1.78 mm Hg as compared with placebo [26]. If serum magnesium is causally related to cardiovascular risk, a modest increase in serum magnesium could have contributed to a reduction in cardiovascular mortality observed among patients with type 2 diabetes in the EMPA-REG OUTCOME trial [19]. However,

the observed changes in serum magnesium levels were, on average, within the physiological range. We do not know what proportion of individuals would have levels above the normal range, and therefore the clinical significance/interpretation of these data is uncertain.

Changes in serum phosphate were also observed for dapagliflozin with a mean increase of 0.04 mmol/l and 0.05 mmol/l for 5 mg and 10 mg, respectively. The effects of increasing serum phosphate may have adverse effects on bone health by increasing secretion of parathyroid hormone, which enhances bone resorption and increases the risk of bone fractures [27]. Although one study showed that canagliflozin was associated with a decrease in bone mineral density at total hip in type 2 diabetes patients [28], the effect of SGLT2 inhibitors on fractures are still uncertain. It is interesting to find that serum sodium levels appear to differ by SGLT2 inhibitor type with a mean reduction of 0.36 mmol/l for canagliflozin 300 mg and a mean increase of 0.31mmol/l for empagliflozin 25 mg. However, the clinical significant of small change in serum sodium levels less than 0.5 mmol/l was still unclear.

Some limitations of our meta-analysis (e.g., low number of patients included in each SGLT2 inhibitor and statistically significant between-study heterogeneity) merit discussion, which reduced the strength of the evidence. In addition, we were unable to calculate the proportion of individuals who would have an abnormal electrolyte levels through taking SGLT2 inhibitors due to limit information from trials.

In summary, SGLT2 inhibitors marginally increased serum magnesium levels among patients with type 2 diabetes. Dapagliflozin increased serum phosphate levels, but the

serum sodium levels appeared to differ between empagliflozin and canagliflozin. Further investigation is required to examine the clinical significance of changes in serum magnesium, phosphate, and sodium levels caused by SGLT2 inhibitors in patients with type 2 diabetes, especially those with several co-morbid chronic diseases.

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Duality of interest The authors declare that there is no duality of interest associated with this manuscript.

Contribution Statement HT and YS designed the study. HT and XZ identified and acquired reports of trials and extracted data. HT and XZ performed all data analyses, checked for statistical inconsistency, and interpreted data. HT, XZ, JZ, YL, LDG, SZ, and YS contributed to data interpretation. HT drafted the report, and all other authors (XZ, JZ, YL, SZ, LDG, and YS) critically reviewed the report. HT, XZ, JZ, YL, LDG, SZ, and YS approved the final manuscript. YS is responsible for the integrity of the work as a whole.

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Figure Legend:

Fig. 1 Meta-analysis of standardized mean difference and 95% confidence interval in change in serum magnesium levels for each SGLT2 inhibitor versus placebo, stratified by dose.

The WMD for canagliflozin was calculated as mean percent change from baseline (%) (a), and the other SGLT2 inhibitors were calculated as mean change from baseline (mmol/l) (b). The study of Rosenstock (2015) was excluded in the meta-analyses because of zero standard deviation. Note: weights are from random effects analysis. WMD, weighted mean difference; CI, confidence interval; N, number of patients; SD, standard deviation.

Table 1. Meta-analysis of weighted mean difference and 95% confidence interval in change of serum calcium, phosphate, potassium and sodium for each SGLT2 inhibitor versus placebo, stratified by dose.

SGLT2 inhibitor	Serum calcium levels				Serum phosphate levels				Serum potassium levels				Serum sodium levels			
	n	N[c]	WMD (95%CI)	Het-I^2% (95%CI)	n	N[c]	WMD (95%CI)	Het-I^2% (95%CI)	n	N[c]	WMD (95%CI)	Het-I^2% (95%CI)	n	N[c]	WMD (95%CI)	Het-I^2% (95%CI)
Canaglilfozin[a]																
100 mg	-	-	-	-	2	541	1.60 (-6.33,9.54)	90.3	3	1019	0.15 (-0.88,1.17)	0（0,90）	2	541	-0.22 (-0.61,0.17)	34.3
300 mg	-	-	-	-	2	541	2.56 (-3.32,8.44)	83.2	3	1014	0.61 (-1.45,2.27)	72 (5, 92)	2	541	-0.36 (-0.68,-0.05)	0
Dapagliflozin[b]																
2.5 mg	2	535	0.03 (-0.02,0.08)	63	2	535	0.01 (-0.02,0.04)	0	2	535	-0.02 (-0.20,0.15)	69.5	2	535	0.05 (-0.68,0.77)	21.8
5 mg	2	543	0.00 (-0.03,0.03)	20.9	2	543	0.04 (0.01,0.06)	0	2	543	-0.08 (-0.17,0.01)	2.1	2	543	0.49 (-0.11,1.08)	0
10 mg	3	712	0.00 (-0.03,0.03)	46.6 (0, 84)	3	712	0.05 (0.02,0.09)	43.3 (0, 83)	3	712	-0.04 (-0.20,0.13)	64.6	2	532	0.37 (-0.31,1.06)	0
Empagliflozin[b]																
10 mg	9	7578	0.00 (-0.01,0.01)	0 (0,65)	9	7578	0.02 (-0.01,0.05)	93 (89,96)	9	7578	0.01 (-0.02,0.04)	65.2 (29, 83)	9	7578	0.19 (-0.03,0.49)	77 (56,88)
25 mg	9	7552	0.00 (-0.01,0.01)	0 (0, 65)	9	7552	0.02 (-0.01,0.05)	93 (89, 96)	9	7552	-0.00 (-0.04,0.04)	76.7 (56,88)	9	7552	0.31 (0.04,0.58)	86.1 (75,92)
Ipragliflozin[b]																
50 mg	1	170	-0.01 (-0.04,0.02)	-	1	170	0.13 (-0.02,0.28)	-	1	170	0.02 (-0.08,0.12)	-	1	170	0.00 (-0.62,0.62)	-

[a] mean percent change from baseline (%)

[b] mean change from baseline (mmol/l)

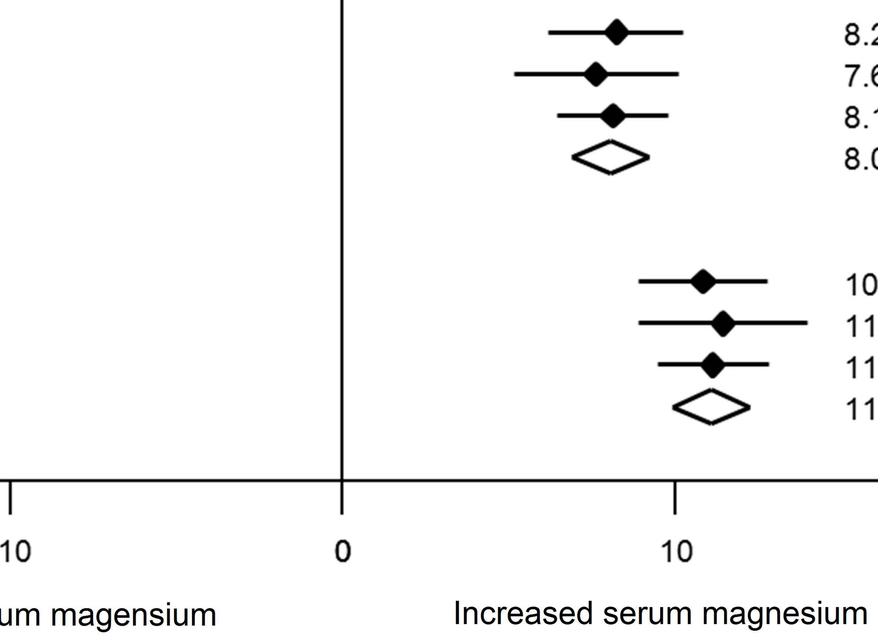
[C] safety analyses set

- data not available

n, number of trials; N, number of patients; SGLT2, Sodium glucose cotransporter 2; WMD, weighted mean difference; CI, confidence interval; Het, heterogeneity

a

Study	WMD (95% CI)	*n*, mean (SD); SGLT2 inhibitor	*n*, mean (SD); Placebo	% Weight
Canagliflozin				
100 mg				
Wilding et al (2013) [5]	8.20 (6.18, 10.22)	157, 7.1 (10.3)	156, -1.1 (7.8)	31.50
Forst et al (2014) [6]	7.60 (5.13, 10.07)	113, 7.6 (8.9)	115, 0 (10.1)	21.14
Bode et al (2015) [7]	8.10 (6.45, 9.75)	241, 6.8 (9.5)	237, -1.3 (8.9)	47.36
Subtotal (I^2=0.0%)	8.03 (6.89, 9.16)	511	508	100.00
300 mg				
Wilding et al (2013) [5]	10.80 (8.87, 12.73)	156, 9.7 (9.5)	156, -1.1 (7.8)	34.39
Forst et al (2014) [6]	11.40 (8.85, 13.95)	114, 11.4 (9.6)	115, 0 (10.1)	19.65
Bode et al (2015) [7]	11.10 (9.43, 12.77)	236, 9.8 (9.6)	237, -1.3 (8.9)	45.96
Subtotal (I^2=0.0%)	11.06 (9.92, 12.19)	506	508	100.00



b

Study	WMD (95% CI)	*n*, mean (SD); SGLT2 inhibitor	*n*, mean (SD); Placebo	% Weight
Dapagliflozin				
2.5 mg				
Wilding et al (2012) [8]	0.20 (0.14, 0.26)	202, 0.08 (0.15)	193, -0.12 (0.38)	50.35
Bailey et al (2015) [10]	0.04 (-0.02, 0.10)	65, -0.06 (0.16)	75, -0.1 (0.22)	49.65
Subtotal (I^2=92.6%)	0.12 (-0.04, 0.28)	267	268	100.00
5 mg				
Wilding et al (2012) [8]	0.18 (0.12, 0.24)	211, 0.06 (0.17)	193, -0.12 (0.38)	51.14
Bailey et al (2015) [10]	0.05 (-0.02, 0.12)	64, -0.05 (.2)	75, -0.1 (0.22)	48.86
Subtotal (I^2=87.2%)	0.12 (-0.01, 0.24)	275	268	100.00
.				
10 mg				
Wilding et al (2012) [8]	0.21 (0.15, 0.27)	194, 0.09 (.17)	193, -0.12 (0.38)	32.23
Bolinder et al (2014) [9]	0.06 (0.05, 0.07)	89, 0.02 (0.04)	91, -0.04 (0.04)	36.70
Bailey et al (2015) [10]	0.03 (-0.04, 0.10)	70, -0.07 (.19)	75, -0.1 (0.22)	31.07
Subtotal (I^2=92.1%)	0.10 (0.01, 0.19)	353	359	100.00
Empagliflozin				
10 mg				
Rosenstock et al (2014) [11]	0.10 (0.08, 0.12)	186, 0.1 (0.1)	188, 0 (0.1)	12.64
Roden et al (2013) [12]	0.00 (-0.02, 0.02)	224, 0 (0.1)	228, 0 (0.1)	12.80
DeFronzo et al (2015) [13]	0.10 (0.06, 0.14)	135, 0.1 (0.1)	128, 0 (0.2)	10.67
Lewin et al (2015) [14]	0.10 (0.08, 0.12)	135, 0.1 (0.1)	133, 0 (0.1)	12.30
Kovacs et al (2014) [15]	0.00 (-0.02, 0.02)	165, 0 (0.1)	165, 0 (0.1)	12.52
Haring et al (2014) [17]	0.00 (-0.02, 0.02)	217, 0 (0.1)	207, 0 (0.1)	12.75
Haring et al (2015) [18]	0.00 (-0.02, 0.02)	225, 0 (0.1)	225, 0 (0.1)	12.80
Zinman et al (2015) [19]	0.05 (0.04, 0.06)	2345, 0.05 (0.1)	2333, 0 (0.1)	13.52
Rosenstock et al (2015) [20]	(Excluded)	169, 0 (0.1)	170, 0 (0)	0.00
Subtotal (I^2= 95.1%)	0.04 (0.02, 0.07)	3801	3777	100.00
25 mg				
Rosenstock et al (2014) [11]	0.10 (0.07, 0.13)	189, 0.1 (0.2)	188, 0 (0.1)	11.61
Roden et al (2013) [12]	0.00 (-0.02, 0.02)	224, 0 (0.1)	228, 0 (0.1)	12.95
DeFronzo et al (2015) [13]	0.10 (0.06, 0.14)	134, 0.1 (0.1)	128, 0 (0.2)	10.83
Lewin et al (2015) [14]	0.10 (0.08, 0.12)	134, 0.1 (0.1)	133, 0 (0.1)	12.45
Kovacs et al (2014) [15]	0.10 (0.08, 0.12)	168, 0.1 (0.1)	165, 0 (0.1)	12.68
Haring et al (2014) [17]	0.10 (0.08, 0.12)	213, 0.1 (0.1)	207, 0 (0.1)	12.89
Haring et al (2015) [18]	0.00 (-0.02, 0.02)	216, 0 (0.1)	225, 0 (0.1)	12.93
Zinman et al (2015) [19]	0.05 (0.04, 0.06)	2342, 0.05 (0.1)	2333, 0 (0.1)	13.66
Rosenstock et al (2015) [20]	(Excluded)	155, 0 (0.1)	170, 0 (0)	0.00
Subtotal (I^2=94.8%)	0.07 (0.04, 0.09)	3775	3777	100.00
Ipragliflozin				
50 mg				
Lu et al (2016) [20]	0.05 (0.03, 0.08)	87, 0.07 (0.095)	83, 0.015 (0.07)	100.00
Subtotal (I^2 NA)	0.05 (0.03, 0.08)	87	83	100.00